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### Challenges in the implementation of EAACI guidelines on allergen immunotherapy

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# Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy

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## Abstract

**Purpose:** The European Academy of Allergy and Clinical Immunology (EAACI) has produced Guidelines on Allergen Immunotherapy (AIT). We sought to gauge the preparedness of primary care to participate in the delivery of AIT in Europe.

**Funding information**

European Academy of Allergy & Clinical Immunology

This Guideline published by the European Academy of Allergy and Clinical Immunology (EAACI) has drawn on data from a systematic review of the literature, more recent published studies and multitakeholder expert clinical opinion. This Guideline is aimed at healthcare professionals who are encouraged to take the recommendations into account in the context of delivering clinical care. This Guideline is not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

**Methods:** We undertook a mixed-methods, situational analysis. This involved a purposeful literature search and two surveys: one to primary care clinicians and the other to a wider group of stakeholders across Europe.

**Results:** The 10 papers identified all pointed out gaps or deficiencies in allergy care provision in primary care. The surveys also highlighted similar concerns, particularly in relation to concerns about lack of knowledge, skills, infrastructural weaknesses, reimbursement policies and communication with specialists as barriers to evidence-based care. Almost all countries (92%) reported the availability of AIT. In spite of that, only 28% and 44% of the countries reported the availability of guidelines for primary care physicians and specialists, respectively. Agreed pathways between specialists and primary care physicians were reported as existing in 32%-48% of countries. Reimbursement appeared to be an important barrier as AIT was only fully reimbursed in 32% of countries. Additionally, 44% of respondents considered accessibility to AIT and 36% stating patient costs were barriers.

**Conclusions:** Successful working with primary care providers is essential to scaling-up AIT provision in Europe, but to achieve this, the identified barriers must be overcome. Development of primary care interpretation of guidelines to aid patient selection, establishment of disease management pathways and collaboration with specialist groups are required as a matter of urgency.

**KEYWORDS**

barriers, care pathways, educational needs, immunotherapy guidelines, primary care

## 1 | INTRODUCTION

The march of allergy proceeds relentlessly with up to a third of the general population and half of young people suffering from some manifestation of the disease at some stage in their lives.<sup>1</sup> The most prevalent of these conditions are atopic eczema/dermatitis, asthma and allergic rhinitis.<sup>2-5</sup> These result in a significant impact at the personal level because of impaired quality of life, a significant impact on family and friends, on the healthcare system because of increased medical costs and at a societal level because of lost productivity through presenteeism and absenteeism.<sup>6,7</sup> Currently, allergy is often not well recognized and is as a result poorly managed.<sup>8</sup> Patients seek assistance from various sources, often involving considerable expense and inappropriate treatment.<sup>9-11</sup> Primary care professionals (hereafter referred to as PCPs), these including general practitioners, nurses and paediatricians, in some countries,<sup>12</sup> are poorly equipped to deal with the management of allergy, particularly the more complex issues associated with AIT, due to deficiencies in undergraduate and postgraduate training.<sup>13</sup> Previous surveys have revealed a low level of PCPs' self-estimated knowledge or confidence in delivering AIT.<sup>12</sup> To date, there is no care system which delivers comprehensive allergy care in a systematic fashion.<sup>14</sup>

In most cases, the management of allergy comprises allergen avoidance<sup>15</sup> and symptom alleviation by pharmacotherapy. This contrasts with allergen immunotherapy (AIT) which targets the

immunological basis of the disease. It can be used as complementary to or in some cases as an alternative to pharmacotherapy in patients for whom pharmacotherapy is not sufficiently effective or for patients who prefer a disease-modifying treatment over chronic, often lifelong use of symptom relieving drugs.<sup>16</sup> AIT involves the administration of allergen to deviate the immune response from immediate hypersensitivity towards tolerance.<sup>17</sup> Typically, either injection (subcutaneous AIT, SCIT), sublingual AIT (SLIT) or oral AIT (OIT) is used.<sup>18</sup>

The European Academy of Allergy and Clinical Immunology (EAACI) has embarked on a process of formulating comprehensive guidelines for AIT supported by underpinning systematic reviews on the effectiveness, cost-effectiveness and safety of AIT for allergic rhinitis,<sup>19</sup> asthma,<sup>20,21</sup> venom allergy,<sup>22</sup> food allergy<sup>23</sup> and the prevention of allergy and allergic disorders.<sup>24</sup> The EAACI Guidelines on AIT should help to identify patients who are most likely to benefit from this potentially disease-modifying treatment while also highlighting the current gaps in knowledge and service provision.

For comprehensive AIT services to be implemented, a system-wide approach is needed, commencing and ultimately culminating in primary care. This requires an understanding of primary care<sup>25</sup> taking into account the significant regional and national variation in configuration of health services across Europe.<sup>26</sup> AIT needs to be seen in the wider context of overall provision of care for allergic patients, which itself needs to be contextualized within overall healthcare provision.

We have performed a mixed-method, situational analysis of current provision of AIT, comprising of a literature review and surveys, in primary care across Europe. This was done as part of the EAACI AIT Guidelines initiative and aimed to develop a summary of the current deficits in the service delivery of allergy care and AIT across the whole health system. We collected survey data from: (i) GPs and (ii) allergy stakeholders, including patient and specialist organizations. We focused on asthma, allergic rhinitis and venom allergy; we excluded AIT for food allergy and allergy prevention as these are developing areas. Our aim was to summarize the different perspectives on the current capabilities of primary care in the provision of allergy management, in particular AIT. It will build on our previous EAACI position paper<sup>27</sup> and work performed in the UK.<sup>28</sup>

## 2 | METHODS

We developed a mixed-methods approach to assess the current capabilities of AIT provision in primary care and used our findings to draw up a list of recommendations.

### 2.1 | Literature search

To inform our paper, we (DR, EA) performed a focused PubMed literature search (see Online supplement 1 for search strategy). This was supplemented by a (UK) Royal College of General Practitioners Discovery and Medline search. The abstracts were assessed by DR and EA. Papers not written in English, and irrelevant papers were rejected. The remaining papers were read in full. Due to the diversity of papers with few recurring themes, a narrative description of the literature search was undertaken.

### 2.2 | Situational analysis

We undertook a situational assessment using an online questionnaire (see Online supplement 2) to understand the perspectives of stakeholders: (i) general practitioners (GPs), and (ii) stakeholders (specialist allergy societies and patient organizations) in different European countries. We developed a draft survey, which was piloted and, where necessary, revised. There were 12 questions for GPs and 10 questions for stakeholders (see Online supplement). A combination of closed and open-ended questions was chosen to elicit additional information regarding perspectives on strategies to improve uptake of AIT in primary care. The survey was administered through the web-based SurveyXact system. (SurveyXact, Aarhus, Denmark). Invitations to participate in the survey were distributed to European GPs via the International Primary Care Respiratory Group (IPCRG) and World Organization of National Colleges and Associations, Europe (WONCA); to European specialist allergy societies using a list supplied by EAACI; and to European allergy patient support group via the EAACI patient representative contacts list. Data collection took place between December 2016 and February 2017. Two email reminders were sent. Data were analysed using descriptive statistics.

Answers to open-ended questions were coded using content analysis, and illustrative quotes were selected (please see Online supplement 3). We recorded positive answers thereby focusing on presence of services, education, training, reimbursement and barriers. We pooled negative and missing answers as the questionnaire did not always permit us to make a clear distinction between both categories. We have not presented the responses from non-European sources.

## 3 | RESULTS

### 3.1 | Literature search

A total of 59 references were obtained from the combined searches. Of these, 36 were excluded as they provided results of clinical trials, were guidelines or studies analysing cost-effectiveness of AIT. A further 12 papers were duplicates. Eleven papers were thus included; these are summarized briefly below.

One paper addressed care delivery in a generic fashion. It described critical factors for achieving good care, using efficient primary care systems to translate service delivery into high-quality outcomes. The authors described a combination of access, continuity and comprehensiveness.<sup>29</sup> A further paper addressed the variability in allergy care provision in primary care.<sup>30</sup> Two papers focused on the use of specific-IgE in informing patient management as part of a strategy to improve care.<sup>31,32</sup>

Five papers studied perception, knowledge or practice of AIT across various specialist groups, including primary care, paediatricians and ear, nose and throat (ENT) specialists, delivering services in primary care across a large geographical spread.<sup>33-37</sup> These papers also suggested that SCIT was more likely to be prescribed in specialist care and SLIT more commonly prescribed in primary care.

One paper provided an historical description of allergy and how care had progressed over the last 50 years. It highlighted that much still needed to be done to understand the predisposition to atopic disease and identifying the environmental cofactors involved in the "allergic epidemic" and therefore targets for effective primary prevention.<sup>38</sup> The final paper identified common questions in allergy practice gathered from delegates attending a conference on allergy care.<sup>39</sup>

In summary, this literature review described what was already known, namely, that there are major gaps in knowledge and skills in the provision of allergy care, and that these are widespread and not limited to primary care. The literature review also laid bare the paucity of relevant research in primary care settings.

### 3.2 | Situational analysis

#### 3.2.1 | Primary care clinician survey

The GP survey yielded evaluable responses from 132 GPs of which 70 (52%) were from Europe (ie Greece, Ireland, Macedonia, Norway, Poland, Portugal Romania Turkey, UK). The majority of these

responses were from the UK and Romania (53 respondents). The paucity of responses coupled with poor geographical spread led us to create a narrative summary of our findings (online supplement 3.)

Ten per cent reported awareness of any national primary care guidelines; 13% stated that AIT was part of general practice training and 17% said that formal AIT training for GPs was available. 38% stated that GPs were aware that AIT could be administered by subcutaneous and sublingual routes. However, 55% felt that GPs were competent in taking an allergy history.

The greatest barriers perceived for GPs working with AIT were a lack of knowledge and infrastructure (both 79%), concerns about reimbursement policies (68%), time pressures (67%) and suboptimal communication with specialists (55%). Most (67%) respondents stated they were open to collaboration with allergy specialists. These data strongly resonated with other published data<sup>8,13</sup>

### 3.2.2 | Stakeholder survey

The stakeholder survey was sent to 173 specialist allergy societies and allergy patient support groups, with 50 responses (29%) covering 25 European countries. Where more than one set of data was received from one country, the most positive result from that country was included. The rationale for this was to present the best-case scenario. Table 1 gives the positive replies from the 25 European countries to a selected series of questions. From the 36 responses covering the European countries, 18 came from allergy societies, three from patient groups, and 15 were from mixed origin (GPs, individuals, GP societies or not stated).

It would seem that AIT is available in most European countries with the exception of Bosnia and Herzegovina, and Malta. The most common location for administration was in specialist care (84%), but in some countries, administration took place in primary care (20%) or shared care (16%) settings. In 56% of countries there appeared to be a national policy on AIT. The absence of a national policy did not preclude some form of reimbursement, but countries without a national policy were less likely to attract any form of reimbursement.

Comparing answers given to the number of question items generated, some countries clearly had a more comprehensive approach to allergy care (ie Germany, Denmark and the UK) whereas other countries Malta, Portugal and Ireland appeared to have given less consideration to AIT (Table 1).

With regard to barriers to delivering care as assessed by the stakeholders, accessibility (44%) and costs to the patient (including time missed from work and travel costs, 36%) were viewed as the greatest obstacles whereas safety fears (12%) were very low on the list (Table 2).

## 4 | DISCUSSION

The literature review and PCP and stakeholder surveys revealed knowledge and skills gaps coupled with nonexistent or poorly

formulated pathways of training and care. We found that there were more specialist guidelines than primary care ones and more accreditation pathways for specialists than PCPs. Given that specialists would be training primary care colleagues and remain a vital resource, it is important that pathways of care and shared care models are developed. It is to be noted that collaboration between PCPs and specialists was judged to a critical success factor in the Finnish 10 Year Allergy Programme.<sup>40</sup> In reality, patients will present anywhere along a pathway of care. Most AIT is delivered by specialists<sup>41</sup> but this might alter with the availability of SLIT, which is easier to deliver in the community. Adherence with AIT may be facilitated by the involvement of PCPs and pharmacists and may result in cost savings, with specific reference to minimizing time lost from work by patients.<sup>42</sup> Combining shared care pathways with the development of relevant competencies and capacities might increase accessibility to AIT. Tools such as pocket guidelines may also facilitate service delivery.<sup>43</sup>

There are three key areas which need to be addressed. The first is the development of education and training of PCPs. The second key area is diagnosis and stratification of patients into those who can be managed exclusively in primary care and those with more problematic disease who need referral to specialist care. The final area is service delivery and the monitoring of treatment effectiveness at the patient level.

### 4.1 | Education and training

Our survey and other published data<sup>12</sup> suggest that PCPs are not trained to adequately manage allergy patients. Allergy hardly features in most undergraduate medical curricula.<sup>13</sup> There is little allergy training in primary care postgraduate specialist training.<sup>41</sup> There has though been an assessment of training needs<sup>44</sup> and identification of core competencies required<sup>45</sup> which should facilitate an educational process. We suggest that training in allergy and AIT should be included in all undergraduate medical curricula. Furthermore, we suggest that sufficient training in allergy and AIT is included in primary care postgraduate medical specialist training to allow the development of core competencies in the diagnosis and management of common allergic presentations. This would include the use and interpretation of tests used to confirm the presence of sensitization and whether or not this was relevant to the patients' clinical state.<sup>46</sup>

Dialogue between specialist and PCPs should help to improve knowledge and treatment pathways at a local level. The issue of reimbursement of practitioners and patients needs to be recognized as these issues may affect the accessibility to AIT, including those related to travel and missing time from work.

### 4.2 | Diagnosis and stratification of patients

Prior to any other intervention, a secure diagnosis needs to be made. Further, to optimize allergy management patients need to be stratified, probably by disease severity, into those who can be managed exclusively in primary care and those who need referral into specialist care. Characteristically, patients attending their GP or pharmacist

**TABLE 1** Survey. Current situation

	AL	BA	BG	CH	CY	CZ	DE	DK	EE	ES	FI	HR	IE	IT	LV	MT	NL	PL	PO	RO	RS	SE	SL	TR	UK	%
Availability of Immunotherapy	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	92
National Policy				x	x	x	x	x		x	x	x					x	x	x	x		x		x	x	56
National Guidelines																										
Primary Care	x			x					x	x	x					x							x	x	x	28
Specialist Care	x			x		x	x	x	x	x	x									x	x	x				44
Is there an accreditation pathway for Specialists	x	x	x			x	x		x		x									x	x	x			x	40
Is there an accreditation pathway for Primary Care						x						x								x		x				16
Agreed Pathway																										
Shared Care			x	x		x	x	x	x	x	x									x		x			x	44
Referral Criteria	x			x		x	x	x	x	x	x						x		x	x	x	x			x	48
Follow-up monitoring			x	x		x	x	x			x	x					x		x	x	x	x			x	48
Agreed care between professionals			x	x	x	x		x	x						x							x			x	32
Training Pathways						x	x	x	x	x	x	x								x		x			x	40
The location of administration of SCIT																										
Specialist	x	x	x	x	x	x	x	x	x	x		x	x		x		x		x	x	x	x	x	x	x	84
Primary care				x		x	x	x									x		x							20
Shared care						x	x	x				x											x			16
Who makes the decision to discontinue treatment?																										
Specialist	x	x	x		x	x	x	x	x	x	x	x	x		x		x		x	x	x	x	x	x	x	84
Patient			x		x		x	x	x	x	x															28
Primary Care				x																x						12
Is there reimbursement of the product?																										
Any																										
Full reimbursement			x	x		x	x	x	x	x	x	x									x	x	x	x	x	56
Partial reimbursement				x		x	x		x			x									x					32
Is there reimbursement for administration of AIT			x			x	x	x	x	x	x									x	x	x		x	x	24
																										48

AL Albania, BA Bosnia and Herzegovina, BG Bulgaria, CH Switzerland, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, HR Croatia, IE Ireland, IT Italy, LV Latvia, MT Malta, NL the Netherlands, PL Poland, PO Portugal, RO Romania, RS Serbia, SL Slovenia, SE Sweden, TR Turkey, UK United Kingdom.  
X represents a positive response. %: percentage of positive responses.

**TABLE 2** Survey. Barriers

	AL	BA	BG	CH	CY	CZ	DE	DK	EE	ES	FI	HR	IE	IT	LV	MT	NL	PL	PO	RO	RS	SE	SL	TR	UK	%
Fees for time			x				x								x					x						16
Reimbursement barriers to patients travel costs			x				x													x				x		16
Time off work for patients			x			x	x	x												x				x		24
Accessibility			x					x		x			x						x	x		x	x	x		44
Beliefs about efficacy		x					x	x													x			x		28
Beliefs about safety							x	x												x						12
Costs to patients travel time and time off work, etc.			x				x	x		x			x						x	x				x		36

suffer from as yet undiagnosed problems. A thorough history leads to a diagnosis or differential diagnosis. The history should guide the request for investigations.<sup>47</sup> To firmly establish a diagnosis, a physical examination, appropriate to the presenting complaint and investigation(s) is likely to be required, although for some allergic disorders, there may be no relevant physical finding.

According to our survey (data not shown), many GPs across Europe have access to serum specific-IgE testing; in contrast, very few have access to skin prick testing.<sup>48</sup> Small studies confirm that such testing improves the ability to make a diagnosis of allergic and, importantly, of nonallergic diseases.<sup>31,49</sup> There is a clear rationale for using specific-IgE tests in primary care.<sup>31,50</sup> Further work needs to be undertaken around the place and utility of specific-IgE in primary care and how best to educate practitioners in the interpretation of results in the clinical context.<sup>46</sup> This has been identified as a pressing research need by the IPCRG.<sup>51</sup>

### 4.3 | Service delivery and monitoring

Developing vertically integrated care pathways might be one way of developing a process for service delivery.<sup>52</sup> Such a pathway could include community pharmacists to aid in identification of patients; they may also be able to play a role in promoting adherence. The patient journey often commences with the community pharmacist, providing a rationale for including them in any proposed care.<sup>53</sup> A further option to be considered, particularly where specialists are scarce, is the development of a network of GPs with specialist interests (GPwSIs) whose remit would include service provision and local educational initiatives working in close collaboration with specialist mentors.<sup>54,55</sup> This would also present an opportunity to develop a network of care to establish clear communication and shared decision-making.

### 4.4 | Strengths and limitations of the surveys

An exploratory analysis is presented, the first of its kind. The study focuses on the views of primary care clinicians and relevant stakeholders concerning allergy care and AIT and on barriers in this field. The main limitation of this study is the low response rate, particularly in the GP survey. It was difficult to identify appropriate respondents for each country. A substantial number of stakeholder responses came neither from patient groups nor from allergy societies, and thus, responses may not be completely representative of the situation in specific countries although together they provide a reasonable description of the reality across Europe. Finally, although the surveys give a good impression of available services and barriers for GPs in Europe, pooling negative and missing responses and classifying the latter as negative limit the accuracy of the outcome.

### 4.5 | Looking ahead

Based on our findings, we have made some recommendations (see Table 3). Although our findings seem somewhat discouraging, there is room for optimism. Clinical trials in AIT have been successfully



**TABLE 3** Recommendations, barriers and facilitators

Key Recommendations	Barriers	Facilitators	Key References
1. Teaching in allergy and AIT should be included in all undergraduate medical curricula.	<ul style="list-style-type: none"> <li>• Low priority on educational agenda.</li> <li>• Inadequate skills and knowledge in the medical workforce.</li> <li>• Inadequate representation of Allergy in general Undergraduate or Postgraduate curricula.</li> </ul>	<ul style="list-style-type: none"> <li>• Allergy campaigns to raise awareness to governments and patients.</li> <li>• Workforce remodelling with collaborative relationships with specialists.</li> <li>• Clinical system-wide leadership with investment in education and training.</li> </ul>	Potter, 2009. <sup>59</sup> Campbell 2015 <sup>38</sup> Shehata 2006 <sup>13</sup>
2. There should be sufficient training in allergy and AIT included in primary care postgraduate medical specialist training to allow the development of core competencies in the diagnosis and management of common allergic presentations.	<ul style="list-style-type: none"> <li>• Low priority on political agenda with lack of treatment prioritization.</li> <li>• Inadequate health economics data and population-based outcomes.</li> <li>• Inadequate representation of Allergy in general Undergraduate or Postgraduate curricula.</li> </ul>	<ul style="list-style-type: none"> <li>• Workforce remodelling with collaborative relationships with specialists.</li> <li>• Clinical system-wide leadership with investment in education and training.</li> </ul>	Campbell 2015, <sup>38</sup> Tan 2014, <sup>39</sup> Eigenmann 2013 <sup>60</sup> Wallengren 2011 <sup>45</sup>
3. Primary care workers should have access to specific-IgE testing and, if required, have assistance in interpretation of results.	<ul style="list-style-type: none"> <li>• Inadequate skills and knowledge in the medical workforce.</li> <li>• Poor understanding of diagnostic tests in primary care used in the assessment and diagnosis of allergy.</li> <li>• Lack of clear care pathways and referral criteria.</li> <li>• Heterogeneous reimbursement policies for investigations and their administration.</li> <li>• Clinical system-wide leadership with investment in education and training.</li> </ul>	<ul style="list-style-type: none"> <li>• System-wide healthcare delivery mirroring patient journey from pharmacists through to specialists.</li> <li>• Harmonization of reimbursement policies.</li> </ul>	Pelone 2013. <sup>29</sup> Hansen 2010, <sup>30</sup> Dranitsaris 2014. <sup>42</sup> Ellis 2012. <sup>44</sup> Bousquet 2015 <sup>61</sup>
4. There is a need to develop and implement vertically integrated care pathways to improve delivery of allergy care and AIT. This could include clinical decision support systems. It may involve the development of intermediate level GPs with a specialist interest in allergy.	<ul style="list-style-type: none"> <li>• Lack of clear care pathways and referral criteria.</li> <li>• Inadequate health economics data and population-based outcomes.</li> <li>• Heterogeneous reimbursement policies for products and their administration.</li> </ul>	<ul style="list-style-type: none"> <li>• Allergy campaigns to raise awareness to governments and patients.</li> <li>• System-wide healthcare delivery mirroring patient journey from pharmacists through to specialists.</li> <li>• Practice nurses involved in delivery of care, under supervision, allowing flexibility of approach delivering care closer to home.</li> </ul>	Diwakar 2017. <sup>14</sup> Smith 2009. <sup>47</sup> Fromer 2014. <sup>50</sup> Bousquet 2016. <sup>63</sup> Yao 2015, Flokstra - de Blok 2017. <sup>64</sup> Ryan 2005 <sup>54</sup> Yao <sup>62</sup>
5. Develop specific recommendations to aid identification, stratification and referral criteria to enable effective referrals from primary or specialist care.	<ul style="list-style-type: none"> <li>• Low priority on political agenda with lack of treatment prioritization.</li> <li>• Inadequate skills and knowledge in the medical workforce.</li> <li>• Lack of clear care pathways and referral criteria.</li> </ul>	<ul style="list-style-type: none"> <li>• Workforce remodelling with collaborative relationships with specialists.</li> </ul>	Haahtela 2008 <sup>40</sup> Ryan 2017 <sup>12</sup>

carried out in primary care, demonstrating proof of concept.<sup>56,57</sup> It is of further interest that in a real-life study of AIT adherence carried out in the Netherlands that adherence and persistence was higher

amongst patients of GPs than those of allergists or other specialists.<sup>58</sup> The development of pathways of care should facilitate the delivery of high-quality effective services and improve patient selection. These



will vary from health system to health system depending on existing configuration, but are likely to have similar themes. Such pathways would aim to establish a register of those who had received AIT to facilitate identification of type and severity of side-effects as well as permit the assessment of effectiveness of AIT in different patient types which would ultimately aid in patient selection. This would be facilitated by the development of a template which would permit uniformity of coding and clinical parameters entered. This should incorporate a mechanism whereby primary care can report safety issues and adverse effects via a web-based registry system. In addition, network of care with specialists and primary care professionals needs to be developed to establish clear communication and shared decision-making. If, as is happening in some countries, PCPs commence immunotherapy without specialist referral, they should ensure that the products used have proven safety and efficacy.

## 5 | CONCLUSIONS

We have undertaken this work to explore how the EAACI Guidelines on Allergen Immunotherapy for the prevention and management of allergic conditions might be implemented in primary care. The findings from this mixed-methods evaluation strongly suggest that European primary care providers are suboptimally positioned to identify and manage those who are most likely to benefit from AIT. We have identified a number of important barriers—including educational and training, infrastructural and financial—that need to be overcome in order to scale up AIT delivery across Europe. In order to encourage the successful adoption of AIT as a mainstream therapy, there needs to be wide spread publicity concerning its effectiveness. Healthcare provision has great heterogeneity across Europe: the generic recommendations made in this paper will therefore need to be interpreted and tailored in line with local healthcare policies and priorities. Commissioners of health services and politicians need to be made aware of potential benefits and ultimately cost savings in line with the triple aim of health care: better patient experience, improving the health of populations and reducing the cost of health care.

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## CONFLICTS OF INTEREST

Ryan D: Dr. Ryan reports personal fees from MEDA, Stallergenes, Thermo Fisher, AZ, Chiesi, Novartis and Teva, outside the submitted work; Dr. Ryan is Consultant Strategic Clinical Advisor, Optimum Patient Care, President, Respiratory Effectiveness Group; and Chair, Primary Care Interest Group, EAACI. Gerth van Wijk R: Dr. Gerth van Wijk reports personal fees from ALK-Abello, Circassia and Allergopharma, during the conduct of the study. Angier E: Dr Angier reports previous advisory board member on one occasion for

Stallergenes, Meda and Schering Plough; Dr Angier has been sponsored for lecture by Meda, SOSA meeting place at a conference from ALK. Kristiansen M: Dr. Kristiansen has nothing to disclose. Zaman: Mr. Zaman has nothing to disclose. Sheikh A: Dr. Sheikh reports grants from EAACI, during the conduct of the study. Cardona V: Dr. Cardona reports personal fees from ALK, Circassia and Leti, during the conduct of the study, other from Novartis and Shire, grants from Thermofisher, outside the submitted work. Vidal C: Dr. Vidal has nothing to disclose. Warner A: Ms Warner has nothing to disclose. Agache I: Dr. Agache has nothing to disclose. Arasi S: Dr. Arasi reports other from Evidence-Based Health Care Ltd, during the conduct of the study. Fernandez-Rivas M reports grants from the EU, Spanish ministries of Science and Economics: Personal grants from ALK, GSK and Merck and has a patent issued. Halken S Dr. Halken reports personal fees from ALK-Abelló and different companies, for example MEDA, Stallergenes, Allergopharma and ALK-Abelló, outside the submitted work. Jutel M: Dr. JUTEL reports personal fees from ALLERGOPHARMA, ANERGIS, STALLERGENES, from ALK and LETI, outside the submitted work. Lau S: Dr. Lau reports grants from Allergopharma SLIT study grass, personal fees from Merck, during the conduct of the study; grants from German Research foundation DFG, German Ministry of Agriculture and Symbiopharm, outside the submitted work. Pajno G: Dr. Pajno reports grants from Stallergenes, from null, during the conduct of the study. Pfaar O: Dr. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, from Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Biotech Tools S.A., Laboratorios LETI/LETI Pharma, Anergis S.A. and Lofarma, and grants from Biomay, Nuvo and Circassia, and personal fees from Novartis Pharma, MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA2LEN Partner) and Pohl-Boskamp, outside the submitted work. Roberts G: Dr. Roberts reports a patent for the use of sublingual immunotherapy to prevent the development of allergy in at-risk infants issued and his university has received payments for activities I have undertaken, giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck. Sturm G: Dr. Sturm reports grants from ALK-Abello, and personal fees from Novartis, Bencard and Stallergenes, outside the submitted work; Varga EM: Dr. Varga reports personal fees from ALK-Abello, during the conduct of the study, and personal fees from Lecture fees, ALK-Abello, Stallergenes, Bencard, Allergopharma, MEDA, Nutricia, Steering Committee Member, outside the submitted work. van Ree R: Dr. van Ree reports personal fees from HAL Allergy BV and Citeq BV, outside the submitted work. Muraro: Dr. Muraro reports personal fees from Novartis and Meda Mylan, outside the submitted work.

## AUTHOR CONTRIBUTIONS

Ryan D. Retired GP, Honorary Clinical Research Fellow, involved in core group, questionnaire development and literature review and acted as a coordinator and co-author. Angier E. GP with a special

interest in allergy involved in core group, literature review and questionnaire genesis and analysis and acted as a co-author. Gerth van Wijk R, Co-Chair, Professor of Allergology, involved in core group and analysis. Kristiansen M., Associate Professor, Department of Public Health, involved in questionnaire development and analysis. Zaman H., Senior Lecturer in Pharmacy, provided the pharmacists views. Sheikh A., Professor of Primary Care Research and Development, involved in core group and provided overview and guidance. Warner A., Head of Clinical Services, Allergy UK, provided patient perspective. Cardona V., Allergy Specialist, provided overview and comments. Vidal C., Professor of Allergology, provided overview and comments. Van Ree R, Co-Chair, Professor of Molecular and Translational Allergology, involved in core group and wrote the manuscript. The core group provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. Other authors assisted in drafting the article or revising it critically for important intellectual content. Muraro A, Professor of Allergy, acted as a coordinator of the whole guideline process. Iona Agache: Stefania Arasi, Maria Montserrat Fernandez-Rivas, Susanne Halken, Marek Jutel, Susanne Lau, Giovanni Pajno, Oliver Pfaar, Graham Roberts, Gunter Sturm, Eva Maria Varga: all the above named continually reviewed and commented and gave final approval.

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